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STUDY THE ASSOCIATION OF SERUM LEVEL of βHCG AND ESTRADIOL IN THE PATHOGENESIS OF HYPEREMESIS GRAVIDARUM

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ABSTRACT

Background: The precise mechanism underlying hyperemesis gravidarum, a bothersome condition that affects pregnant women, remains unclear, but appears to be multifactorial.

The Purpose: To study the association of serum level of βHCG and Estradiol in the pathogenesis of hyperemesis gravidarum (HG).

Patients and Methods: From the outpatient clinics & emergency department of Al-Zahra' Teaching Hospital for Gynaecology & Obstetrics / Kufa University we recruit forty five pregnant women with hyperemesis gravidarum and forty five normal pregnant women as a control group. Serum levels of βHCG and Estradiol using VIDAS method were measured for patient group and control group. Statistical analysis of the datas was done.

Results: Regarding the forty five pregnant patients with hyperemesis gravidarum, their mean age was 24.96 years, SD ± 4.719 & p-value =0.752, while the control group, their mean age was 25.29 years, SD± 5.225. Twenty six patients of the forty five (57.8 %) were having serum βHCG above the upper limit of the normal pregnancy (their serum βHCG mean was 137909, SD ± 45536 & p-value =0.000), while five of the forty five (11.1 %) pregnant women of the control group were having serum βHCG above the upper limit of the normal pregnancy (their serum βHCG mean was111181, SD ± 44193 & p-value =0.000). Thirty nine patients of the forty five (86.7 %) were having serum Estradiol level more than the upper limit of normal pregnancy (their serum Estradiol mean was 2090, SD ± 1766 & p-value =0.000), while twenty two of the forty five control group (48.9 %) were having serum estradiol level more than the upper limit of normal pregnancy (their serum Estradiol mean was 984, SD ± 263 & p-value =0.000).

Conclusion: High serum levels of βHCG and Estradiol are associated with hyperemesis gravidarum.

KEYWORDS: Hyperemesis Gravidarum, Pathogenesis, βHCG, Estradiol

INTRODUCTION

Nausea and vomiting in pregnancy is common, and hyperemesis gravidarum is the most severe intractable form of it that leads to volume depletion, electrolytes and acid-base imbalances, ketosis, weight loss, nutritional deficiencies, and some time even death. It affects 0.3-2% of pregnancies[(1)]. It has a pervasive detrimental impact on women's family, social and professional life and are a major complaint in 70-80% of pregnancies[(2)]. The typical onset is between 4 and 8 weeks of gestation, which could last for up to the 14th to 16th weeks[(2)], peaks at 11-13 weeks, and resolves in most cases by 12-14 weeks. In 1-10% of pregnancies, symptoms may continue beyond 20-22 weeks[(3, 4)].

The cause of hyperemesis gravidarum remains unknown, although some of the proposed mechanisms like hormonal mechanisms, emotional factors and H. pylori infection can provide a reasonable explanation, but a conclusive evidence for any single cause remains unconvincing[5].

βHCG is considered one of the aetiological factor for the development of hyperemesis gravidarum as hyperemesis gravidarum incidence highest with the peak level of βHCG. In particular βHCG levels found to be elevated in twin and molar pregnancies (likely since HCG levels very high) and a viable intrauterine pregnancy should always be documented in patients with hyperemesis [6,7]. The mechanisms by which βHCG can cause hyperemesis gravidarum was not clear, but, it may disturb the motility of upper gastrointestinal tract (GIT) by stimulating the intrinsic hormone of the gut, or acting as the thyroid stimulating hormone(TSH) [8].

Many hypothesis suggest that elevated estrogen levels are responsible for excessive vomiting in pregnancy, It has been suggested that patients with hyperemesis are probably more sensitive to oestrogen effects than asymptomatic pregnant women and this is consistent with the observation that estrogen therapy can cause nausea

Hyperemesis gravidarum appears to be related to high or rapidly rising serum estrogen level especially in women having female fetus or in those with higher body mass index, first pregnancy and undescended testicles in the foetus [9].

The placenta early in pregnancy produce high estrogen levels which is responsible for increase water retention and protein synthesis, decreased gastric motility and gastric secretion is reduced resulting in reduced gastric emptying, with the a shift in pH of the gastrointestinal tract (GIT) which may lead to the manifestation of a subclinical Helicobacter pylori infection, which is also attributed to the pathogenesis of hyperemesis gravidarum[10]. However, other studies reported negative results regarding the association between elevated oestrogen levels and the development of hyperemesis.

PATIENTS AND METHODS

Study Objectives

To evaluate the role of βHCG and Estradiol in the pathogenesis of hyperemesis gravidarum (HG).

Overall Study Design

This was a randomized clinical trial carried out from March -2011 till September -2011 on 45 pregnant women presenting with hyperemesis gravidarum and compare them with the same number of healthy pregnant as a control group, attending the Al-Zahra' Teaching Hospital of Gynaecology & Obstetrics at Al- Najaf city, Iraq after their written consent.

Participant, Recruitment and Randomization

The mean age forty five pregnant women was 24.96 years, SD ±4.719 and p-value = 0.752, with a gestational age ranging from 6-13 weeks, their gestational age mean was 10.64 months, SD ± 2.047 & p-value =0.057, presenting with hyperemesis gravidarum were recruited from Al-Zahra' Teaching Hospital of Gynaecology & Obstetrics /Kufa University from March -2011 till September -2011. Forty five normal pregnant women were used as a control group (their age mean was 25.29 years & SD ± 5.225), their gestatinal ages (6-13 weeks), their gestatinal age mean was 9.56 and SD± 3.188. After full history, general and local examinations and ultrasound scanning which done for both the patients group & the control group exclusion of any associated medical disorders such as intracranial disorders, peptic ulcer, drug history as nonsteroidal anti-inflammatory drugs (NSAIDs), urinary tract infection, hyperthyroidism, hepatic disorders, in addition to the exclusion of other obstetric causes for hyperemesis as multiple and molar pregnancy.

Urine analysis for ketone bodies was done for detection of starvation ketosis. Venus blood samples were taken from patient group and control group (10ml). After centrifugation of the venus blood samples, 4 milliliters were sent for measurement serum level of βHCG and Estradiol. Also, two milliliters of the centrefugated venus blood were sent for measurement of renal functions and two milliliters were sent for measurement of liver functions.

Among the forty five pregnant patients with hyperemesis gravidarum (patient group), there were fourteen (31 %) patients with severe symptoms being admitted to the ward& treated with intravenous fluids (Normal saline, Ringer's solution), antiemetics (Metoclopramide ampule of 10 mg, Prochlorperazine ampule of 12.5 mg), vitamine B_6 (Pyridoxine 10-25mg thrice / day, which can be increased up to 200mg /day) supplement, cyclizine tablets 25-50mg qd /day and corticosteroids (Betamethasone vials 4mg and 8mg). Hospital stay ranged two -to- four days.

Patients with mild and moderate symptoms (69 %) were treated in the emergency department by giving them intravenous fluid, antiemetics and vitamine supplements.

Serum Levels of βHCG and Estradiol

Serum levels of βHCG and Estradiol were measured using VIDAS method. Serum level of Estradiol (Serum Estradiol of normal pregnancy ranges from 900-1200 pg / ml) more than 1200 pg /ml was considered higher than normal**.**

THE RESULTS

The patient group (forty five) with hyperemesis gravidarum included twenty one (46.6 %) primigravidae and twenty four (53.4 %) multigravidae, their ages ranged from 17 – 35 years (mean 24.96 & SD ±4.719). None of them had a history of previous peptic ulcer nor duodenal ulcer. Thirteen of the twenty four multigravidae had a history of hyperemesis in previous pregnancies.

The control group (forty five) included thirteen (28.8 %) were primigravidae and thirty two (71.2 %) were multigravidae, their ages ranged from 15 - 35 years (mean was 25.29 & SD ± 5.225).

Ketone bodies in the urine were positive in all hyperemesis patient group, while ketone bodies in the urine (positive) in only five pregnants of the control group.

Regarding renal function and liver function there was no significant statistical changes between patient group and control group.

The serum βHCG and Serum Estradiol in the patient group & the control group are shown in Table NO. 1 and 2.

Table 1 (Serum βHCG)

Table 1: Serum HCG in the Patient Group & the Control Group

Parameters	The Patient Group (n=45)					The Control Group (n=45)			
	n=45	%	Mean	± SD	p-value	n=45	%	Mean	± SD
βHCG: Above the range of normal pregnancy.	26	57.8	173909.5	± 45536.4	0.000	5	11.1	111181.1	± 44193.1
Within range of normal pregnancy.	19	42.2	*			40	88.9	*	

This table shows the level of serum βHCG in both groups. We found that twenty six of forty five pregnant patients (57.8 %) were having serum HCG above the upper limit of the normal pregnancy (their serum βHCG mean= 173909, SD± 45536 & p-value =0.000). Only five pregnant women of the fortyfive of the conrol group (11.1 %) were having serum βHCG above the upper limit of the normal pregnancy (their serum HCG mean= 111181 & SD± 44193). Sixteen of the twenty six (61.5 %) patients with hyperemesis gravidarum were primigravidae, while only one of five (20 %) pregnant women in the control group having serum βHCG above the upper limit of the normal pregnancy was a primigravida.

Table 2 (Estradiol)

Table 2: Serum Estradiol of the Patient Group & the Control Group

Parameters	The Patient Group (n=45)					The Control Group (n=45)			
	n=	%	Mean	± SD	p-value	n=	%	Mean	± SD
Estradiol: Above the Range Pregnancy.	**39**	**86.7**	**2090.4**	**± 1766.6**	**0.000**	**22**	**48.9**	**984.7**	**± 263.2**
Within Range of Normal Pregnancy.	**6**	**13.3**	*****			**23**	**51.1**	*****	

Table -2- shows that thirty nine of the forty five (86.7%) patients with hyperemesis gravidarum were having serum Estradiol above the upper limit of the normal pregnancy (their serum HCG mean= 2090, SD± 1766 & p-value =0.000). Ninteen of the thirty nine (48.7 %) of the patients with hyperemesis gravidarum and having serum Estradiol above the upper limit of the normal pregnancy, were primigravidae. Twenty two of the forty five (48.9 %) pregnant women in the control group were having serum Estradiol above the upper limit of the normal pregnancy (their serum βHCG mean= 984, SD±263 & p-value =0.000), only eight of them (36.6 %) were primigravidae.

DISCUSSIONS

It is well known that nausea and vomiting is associated with changes in endocrine secretion levels following gestation. As with rises in serum βHCG level and with rapidly increasing serum estrogen levels, the symptoms of nausea and vomiting appear[(11)].

Regarding serum βHCG, in our study we found 26 out of 45 (57.8 %) of patient group were having serum level of βHCG above the upper limit of the normal pregnancy(173909.5±45536.4 and p= 0.000), while only five out of forty five (11.1 %) of the control group were having serum level of HCG above the upper limit of the normal pregnancy (111181.13±44193.1) as Table 1 shows. This was agrees with study of Goodwin *et al*. [(12)] who found that Human chorionic gonadotropin was higher among hyperemesis subjects compared to controls (97 ± 8 IU/mL, 29 ± 2 IU/mL, $p < 0.001$), this finding, strengthens the association of hyperemesis with abnormal metabolism of hCG, but there was a weak correlation between HCG and Free T4 and TSH.

The proposed mechanisms by which βHCG can cause hyperemesis gravidarum probably by its stimulating effect on the secretory processes in the upper gastrointestinal tract (GIT) or by stimulation of thyroid function as it is structurally similarity toThyroid Stimulating Hormone [(6)].

M.F.G. Verberg et al reviews a twenty-three studies done to investigate the relation between HCG and hyperemesis gravidarum, all of these studies were prospective comparative with pregnant control group and eight out of fifteen matched for gestational age. 11 studies published since 1990 out of the 15, showed a significantly higher level of serum HCG in hyperemesis gravidarum patients than in control group. Supporters of this theory have tried to explain the dissenting results by differences in the assay methodology used[(2)].

Diversity in assays to investigate the HCG level has been used to compare HCG levels between hyperemesis gravidarum patients and control group, and HCG assays can differ remarkably in their ability to detect HCG subunits, isoforms or metabolites (Berger *et al*., 1993; Cole, 1997)[(3,13)].

As HCG is considered one of the most endocrine factor which that is responsible for the pathogenesis of HG based on finding increment of its production in molar and multiple pregnancies, in addition to the great association between the time of its peak level during pregnancy (around 9 weeks gestation) and the peak of hyperemesis[(14)]. However, some pregnant women do not experience nausea and vomiting despite elevated HCG-levels and patients with chorionic carcinoma may not had vomiting. These controversies may be related to the varying biological activity of different isoforms of HCG, in addition to the individual sensitivity to the emetogenic stimuli and the hormone-receptor interactions which may modify its action[(15)].

Several studies have been published to confirm abnormal estradiol (E2) levels in patients with HG. in our study, we found that thirty nine out of forty five (86.7 %) of pregnant patients with hyperemesis gravidarum were having serum level of Estradiol above the upper limit of the normal pregnancy (2090.4±1766.6 & p=0.000), while only twenty two out of forty five (48.9 %) of the pregnant women in the control group were having serum level of Estradiol above the upper limit of the normal pregnancy (984.7± 263.2. Yoneyama *et al.* [(11)] and Goodwin *et al* [(12)] found significantly elevated mean estrogen levels in HG patients. However, in a retrospective survey, a strong correlation has been observed between women suffering from nausea in pregnancy and nausea during the use of oral contraceptives, an estrogen-related side effect, supporting the hypothesis that HG patients might be more sensitive to the effects of estrogens[(16)]. A prospective study done by Lagiou et al[(9)] on 209 women having nausea and vomiting found that estradiol levels were positively correlated with nausea and vomiting in pregnancy. Other study done by Schiff MA et al report that nausea and vomiting in pregnancy caused by increased levels of oestrogen and oestradiol. Hence, severe nausea and vomiting in the presence of a female foetus *in utero* is explained by a raised concentration of oestrogen[(17)]. On the other hand, pregnancies induced by controlled ovarian stimulation (COS) in assisted reproduction techniques (ART) may not associated with a higher incidence of hyperemesis gravidarum in spite of very high circulating estrogen levels[(2)].

CONCLUSIONS

High level of βHCG & Estradiol are associated with HG.

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